PATENTTI- JA REKISTERIHALLITUS
NATIONAL BOARD OF PATENTS AND REGISTRATION

537, 177

PCT / FI 2004 / 000004

Helsinki 31.8.2005

E T U O I K E U S T O D I S T U S
P R I O R I T Y D O C U M E N T

Hakija Applicant	**Oy Juvantia Pharma Ltd** **Turku**
Patenttihakemus nro Patent application no	**20030026**
Tekemispäivä Filing date	**08/01/2003**
Kansainvälinen luokka International class	**C07D233/58**

CERTIFIED COPY OF PRIORITY DOCUMENT

Keksinnön nimitys
Title of invention

"Process for preparing substituted imidazole derivatives and intermediates used in the process"
(Menetelmä substituoitujen imidatsolijohdannaisten valmistamiseksi ja menetelmässä käytettäviä välituotteita)

Täten todistetaan, että oheiset asiakirjat ovat tarkkoja jäljennöksiä Patentti- ja rekisterihallitukselle alkuaan annetuista selityksestä, patenttivaatimuksista ja tiivistelmästä.

This is to certify that the annexed documents are true copies of the description, claims and abstract, originally filed with the Finnish Patent Office.

Marketta Tehikoski
Apulaistarkastaja

Maksu 50 €
Fee 50 EUR

Maksu perustuu kauppa- ja teollisuusministeriön antamaan asetukseen 1142/2004 Patentti- ja rekisterihallituksen maksullisista suoritteista muutoksineen.

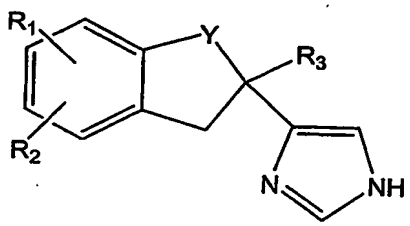
The fee is based on the Decree with amendments of the Ministry of Trade and Industry No. 1142/2004 concerning the chargeable services of the National Board of Patents and Registration of Finland.

Osoite: Arkadiankatu 6 A, P.O.Box 1160, FIN-00101 Helsinki, FINLAND
Puhelin: 09 6939 500, Telephone: + 358 9 6939 500
Telefax: 09 6939 5328, Telefax: + 358 9 6939 5328

PROCESS FOR PREPARING SUBSTITUTED IMIDAZOLE DERIVATIVES AND INTERMEDIATES USED IN THE PROCESS

FIELD OF THE INVENTION

The present invention relates to a new process for preparing substituted imidazole derivatives of formula (I) and acid addition salts thereof,



(I)

in which formula Y is $-CH_2-$ or -CO-, R_1 is H, halo or hydroxy, R_2 is H or halo and R_3 is H or lower alkyl.

The invention also relates to intermediates used in the process and to their preparation.

BACKGROUND OF THE INVENTION

The compounds of the above-mentioned formula (I) are highly selective and long-acting antagonists of α_2-adrenoceptors and they have a good peroral bioavailability. The compounds are especially valuable in the treatment of cognitive disorders. Compounds of formula (I) have been described in patent publication EP 0 618 906 B1. Specific examples of such compounds are 4-(2-ethyl-5-fluoro-2,3-dihydro-1H-inden-2-yl)-1H-imidazole and 4-(5-fluoro-2,3-dihydro-1-inden-2-yl)-1H-imidazole.

The above-mentioned publication EP 0 618 906 B1 also discloses methods of preparing compounds of formula (I). Said methods relate to various ways of modifying the substituents in the benzene moiety of the indan ring system. There is no disclosure of a total synthesis which would lead to the desired compounds in good yield.

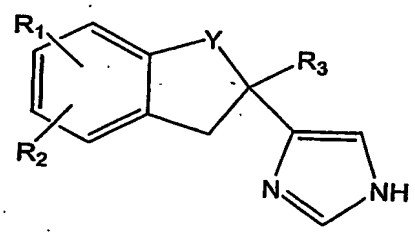
Publication EP 0 310 745 B1 discloses a process for preparing compounds of formula (I), wherein the last step of the process comprises the use of formamide for the formation of the imidazole ring. The use of forma-

mide, however, requires severe reaction conditions, which should be avoided in connection with industrial production in large scale.

Although the single steps of the process according to the present invention are known as such (see e.g. EP 0 146 228 B1), it has now surprisingly been found that compounds of formula (I) can be prepared, also in large scale, in very good yields by using the synthesis route described below.

SUMMARY OF THE INVENTION

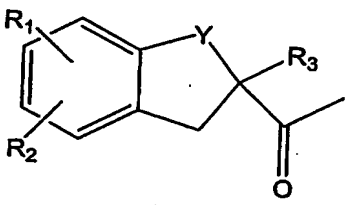
The present invention relates to a process for preparing substituted imidazole derivatives of formula (I) and acid addition salts thereof



(I)

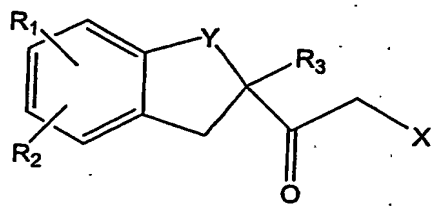
in which formula Y is $-CH_2-$ or $-CO-$, R_1 is H, halo or hydroxy, R_2 is H or halo and R_3 is H or lower alkyl, comprising the steps of

a) halogenating a compound of formula (II)



(II)

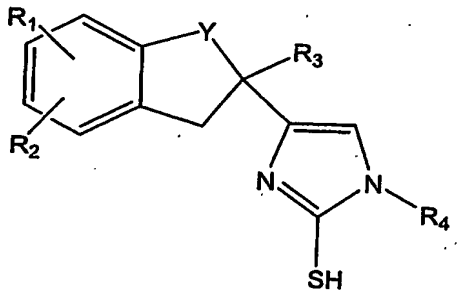
wherein Y, R_1, R_2 and R_3 are as defined above, to obtain a compound of formula (III)



(III)

wherein Y, R_1, R_2 and R_3 are as defined above and X is halo,

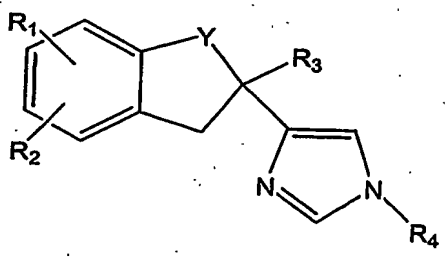
b) reacting the compound of formula (III) thus obtained with an amine of formula R_4NH_2, wherein R_4 is an easily removable leaving group, and an alkali metal thiocyanate, to obtain a compound of formula (IV)



(IV)

wherein Y, R_1, R_2, R_3 and R_4 are as defined above,

c) removing the mercapto group from the compound of formula (IV) to obtain a compound of formula (V)



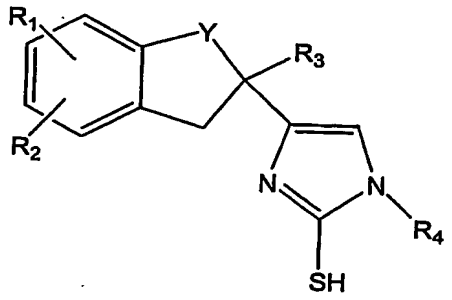
(V)

wherein Y, R_1, R_2, R_3 and R_4 are as defined above,

d) removing the group R_4 from the compound of formula (V) to obtain a compound of formula (I), and, if desired,

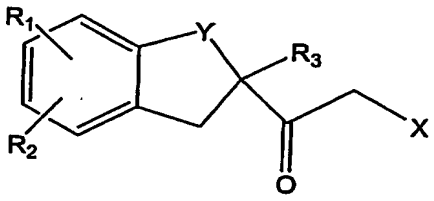
e) converting the resulting compound of formula (I) into an acid addition salt thereof.

Further the invention relates to a process for preparing a compound of formula (IV)



(IV)

wherein Y is $-CH_2-$ or -CO-, R_1 is H, halo or hydroxy, R_2 is H or halo and R_3 is H or lower alkyl, comprising reacting a compound of formula (III)



(III)

wherein Y, R_1, R_2 and R_3 are as defined above and X is halo, with an amine of formula R_4NH_2, wherein R_4 is an easily removable leaving group, and an alkali metal thiocyanate.

The invention also relates to intermediate compounds (IV) and (V) wherein Y, R_1, R_2, R_3 and R_4 are as defined above.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention a compound of formula (II) is, in step a), halogenated with a halogenating agent to obtain a compound of formula (III), where X is a halogen, e.g. Br, Cl or I. A preferred halogenating agent is Br_2. The reaction is suitably carried out in a solvent, such as an alcohol, e.g. methanol, at room temperature or below. A suitable temperature is –8 to +25, preferably –8°C to –5°C.

In step b) the compound of formula (III) obtained in step a) is reacted with an amine of formula R_4NH_2 where R_4 is a easily removable leaving

group, and an alkali metal thiocyanate to obtain a mercapto compound of formula (IV). The reaction is suitably carried out in a solvent, such as as an alcohol, e.g. ethanol or butanol, at an elevated temperature, preferably at reflux temperature. The amine for the reaction may be one where R_4 is aralkyl, preferably benzyl. A preferred alkali metal thiocyanat is potassium thiocyanate.

In step c) the mercapto group is removed from the compound of formula (IV) obtained in step c) to obtain a compound of formula (V). The reaction is suitably carried out in the presence of a catalyst, e.g Raney-Nickel, at a temperature of 40°C to 90°C, preferably 40 °C to 60°C.

In step d) the group R_4 can be removed from the compound of formula (V) obtained in step c) by treating the compound of formula (V) with ammonium formate in the presence of a catalyst, such as Pd/C. Alternatively a catalyst, such as Raney-Nickel, may be used, or R^4 may be removed by hydrogenation in the presence of Pd/C.

The resulting compound of formula (I) may be converted into acid addition salts using methods known per se. Preferred acid addition salts are HCl and HBr.

Preferred compounds of formulae (I) to (V) are those where Y is CH_2, R_1 is F, R_2 is H and R_3 is ethyl.

The process according to the present invention makes it possible to prepare compounds of formula (I) in good yield and in a simple way, e.g. by using lower reaction temperatures, that also is suitable for large-scale production. The known methods result in poor yields and require severe reaction conditions, e.g. high temperatures, which makes large-scale production difficult. For instance, compared to the process using formamide (EP 0 310 745 B1), the process of the present invention using lower temperatures does not create separation or isolation problems relating to great amounts of various impurities that are typically formed in the known formamide process

The following examples illustrate the invention, but are not intended to restrict the scope of the invention.

Example 1

2-bromo-1-(2-ethyl-5-fluoro-indan-2-yl)-ethanone

3,8 g of 2-acetyl-2-ethyl-5-fluoroindan and 35 ml of methanol were placed into a round-bottomed flask equipped with a thermometer, a mechani-

cal stirrer and a dropping funnel. The reaction mixture was cooled in a cooling bath while stirring to a temperature between –5°C and –8°C and 0,7 ml of a Br_2-solution in a small amount of methanol was added dropwise. The cooling bath was removed and the reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was cooled to an temperture between –5°C and –8°C and an additional 0,175 ml of Br_2-solution in a small amount of methanol was added dropwise. The cooling bath was removed and the reaction mixture was stirred at room temperature for an additional 1 to 2 hours. After chromatographic purification using methylene chloride as an eluent 2,51 g of 2-bromo-1-(2-ethyl-5-fluoro-indan-2-yl)-ethanone was obtained as a liquid (yield 69 %).

1H NMR (200 MHz, CDCl3, ppm): 0.85 (3H, t, J 7.6 Hz, CH2CH3), 1.82 (2H, q, J 7.5 Hz, CH2CH3), 2.83-2.93 (2 H, dd, the indan ring H2-1 or H2-3), 3.32-3.46 (2 H, dd, the indan ring H2-1 or H2-3), 4.11 (2H, s, CH2-Br), 6.79-7.10 (3H, m, Ar-H)
HPLC-MS: 285-286-287 (68, M+, Br-isotopes), 205 (72), 187 (100).
UV (Lambda-max): 208 nm (Abs. 1.01020 AU), 271 nm (Abs. 0.27428 AU), 277 nm (Abs. 0.27026 AU).

Example 2

1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole-2-thiol

1,62 g of 2-bromo-1-(2-ethyl-5-fluoro-indan-2-yl)-ethanone was dissolved in 25 ml of ethanol in a glass round-bottomed flask equipped with a mechanical stirrer, a thermometer and a dropping funnel. The reaction mixture was heated while stirring to reflux temperature. 0.366 g of benzylamine dissolved in 5 ml ethanol was added slowly dropwise to the solution. After the addition of benzylamine the mixture was refluxed for one hour. 0,330 g of potassium thiocyanate was added portionwise during 30 minutes and the reaction mixture was refluxed for 2 hours. The reaction mixture was evaporated to dryness and 150 ml ethyl acetate was added and washed with water. The organic phase was dried over Na_2SO_4, filtered and evaporated amounting 1,13 g of 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole-2-thiol (yield 31%). The analytical sample was purified using TLC-plates. The purity was measured by HPLC: 62%. Normally the crude product was used in the following step.

1H NMR (200 MHz, $CDCl_3$, ppm): 0.75 (t, $CH_2C\underline{H}_3$), 1.80 (q, $C\underline{H}_2CH_3$), 2.81-3.30 (m, the indan ring H_2-1 and H_2-3), 5.18 (s, N-$C\underline{H}_2$-Ar), 6.24 (s, -S$\underline{H}$), 6.77-7.09 (m, Ar-H, im-H), 7.23-7.36 (m, Ar-$\underline{H}$-CH_2-N).
HPLC-MS: 353 (100, M+), 221 (29), 187 (12).

Example 3

1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole

7,5 ml of Raney-Nickel prepared according to Vogel, Practical Organic Chemistry, 5th Edition, 1999, Longman, U.K. p. 450-451, was mixed with 20 ml of ethanol under nitrogen atmosphere in a round-bottomed flask equipped with a thermometer and a stirring bar. 500 mg of 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole-2-thiol was dissolved in 10 ml of ethanol and added to the mixture. The reaction mixture was stirred at 40°C for about 10 hours and then the temperature was raised to 60°C for 2 hours followed by cooling to room temperature. The mixture was filtered and the filter (Celite™) was washed with ethanol. The ethanol solution was evaporated to dryness to obtain 151 mg of a crude product. After chromatographic purification using methylene chloride, methylene chloride:methanol (10:1) and methylene chloride:methanol (1:1) as eluents 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole was obtained. The purity was measured by HPLC: 83%.

1H NMR (200 MHz, MeOD, ppm): 0.70 (3H, t, $CH_2C\underline{H}_3$), 1.82 (2H, q, $C\underline{H}_2CH_3$), 2.90-3.01 (2 H, dd, the indan ring H_2-1 or H_2-3), 3.13-3.25 (2 H, dd, the indan ring H_2-1 or H_2-3), 5.10 (2H, s, N-$C\underline{H}_2$-Ar), 6.72-6.87 (3H, m, Ar-H, im-H), 7.05-7.18 (3H, m, Ar-H, Ar-$\underline{H}$-CH_2-N), 7.29-7.32 (3H, m, Ar-$\underline{H}$-CH_2-N), 7.56 (1H, s, im-$\underline{H}$).
HPLC-MS: 321 (100, M+).

Example 4

4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole

53 mg of 1-benzyl-5-(2-ethyl-5-fluoro-indan-2-yl)-imidazole, 20 mg of Pd/C, 51 mg of ammonium formate and 2 ml of ethanol were added under nitrigen atmosphere into a round-bottomed flask equipped with a thermometer

and a stirring bar. The reaction mixture was stirred under at reflux temperature for 6 hours. The mixture was filtered and the filter (Celite™) was washed with ethanol. The reaction mixture was placed back into a round-bottomed flask and additional 20 mg of Pd/C and 51 mg of ammonium formate were added under nitrogen atmosphere and the mixture was heated to reflux temperature and refluxed for 2 hours. Then the mixture was cooled to room temperature and filtered. The filter (Celite™) was washed with ethanol and after evaporation to dryness, whereby 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole was obtained. The analytical sample was purified using TLC-plates. The purity was measured by HPLC: 60%. Normally the crude product was used in the following step.

1H NMR (200 MHz, MeOD, ppm): 0.76 (t, $CH_2C\underline{H_3}$), 1.29 (q, $C\underline{H_2}CH_3$), 2.98-3.22 (m, the indan ring H_2-1 and H_2-3), 6.78-6.94 (m, Ar-H, im-H), 7.09-7.19 (m, Ar-H, im-H).
HPLC-MS: 231 (100, M+).

Example 5

4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole

10 ml of the crude product obtained in Example 3 was placed in a round-bottomed flask equipped with a thermometer and a stirring bar. 1,5 ml of Raney-Nickel in ethanol (Raney-Nickel prepared according to Vogel, Practical Organic Chemistry, 5th Edition, 1999, Longman, U.K. p. 450-451), was added under nitrogen atmosphere. The reaction mixture was stirred at reflux temperature for about 14 hours. After filtration and evaporation crude 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole was obtained.

HPLC-MS: 231 (100, M+).

Example 6

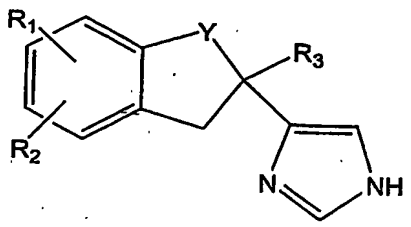
4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole-hydrochloride

A HCl/methanol reagent was prepared by bubbling HCl-gas through methanol. 100 mg of 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole was dissolved in 2 ml methanol in a round-bottomed flask. 2 ml of HCl/methanol reagent (3 M) was added slowly to the solution while stirring. During the addition

the internal temperature of the mixture was kept below 29°C by cooling. The resulting mixture was evaporated to a viscous colourless oil in a temperature between 35°C and 40°C and then it was dissolved in 2ml of acetone at the same temperature. The solution was cooled to a temperature between 10°C and 15°C at which temperature the mixture starts crystallizing. The crystalline material was filtered and washed with cooled acetone and dried in a vacuum oven at 35°C overnight. A second crop was isolated from the mother liquid followed by cooling, filtering and drying as described above. The yield of 4-(2-ethyl-5-fluoro-indan-2-yl)-1H-imidazole-hydrochloride was altogether 87% of the theoretical, m.p. 171 – 173°C.

Claims

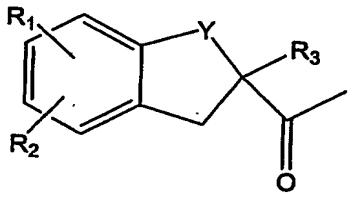
1. A process for preparing substituted imidazole derivatives of formula (I) and acid addition salts thereof



(I)

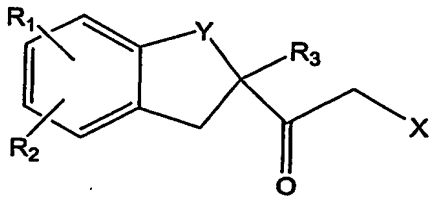
in which formula Y is $-CH_2-$ or $-CO-$, R_1 is H, halo or hydroxy, R_2 is H or halo and R_3 is H or lower alkyl, comprising the steps of

a) halogenating a compound of formula (II)



(II)

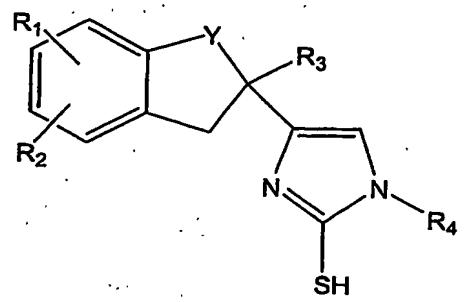
wherein Y, R_1, R_2 and R_3 are as defined above, to obtain a compound of formula (III)



(III)

wherein Y, R_1, R_2 and R_3 are as defined above and X is halo,

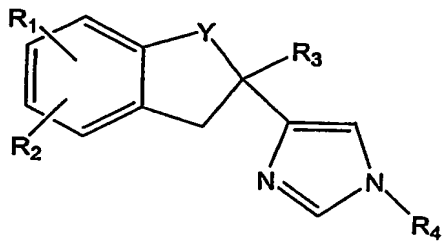
b) reacting the compound of formula (III) thus obtained with an amine of formula R_4NH_2, wherein R_4 is an easily removable leaving group, and an alkali metal thiocyanate, to obtain a compound of formula (IV)



(IV)

wherein Y, R_1, R_2, R_3 and R_4 are as defined above,

c) removing the mercapto group from the compound of formula (IV) to obtain a compound of formula (V)



(V)

wherein Y, R_1, R_2, R_3 and R_4 are as defined above,

d) removing the group R_4 from the compound of formula (V) to obtain a compound of formula (I), and, if desired,

e) converting the resulting compound of formula (I) into an acid addition salt thereof.

2. A process according to claim 1 wherein step a) is carried by reacting a compound of formula (II) with Br_2 in methanol at a temperature of – 8 to +25°C.

3. A process according to claim 1 or 2 wherein step b) is carried out by reacting a compound of formula (III) with benzylamine and potassium thiocyanate.

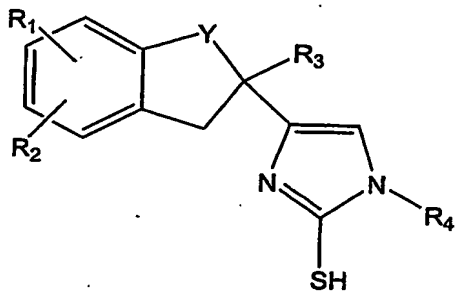
4. A process according to any of claims 1 to 3 wherein step c) is carried out in the presence of Raney-Nickel at a temperature of 40°C to 90°C.

5. A process according to any of claims 1 to 4 wherein step d) is carried out by using ammonium formate in the presence of Pd/C.

6. A process according to any of claims 1 to 4 wherein step d) is carried out by hydrogenation in the presence of Pd/C.

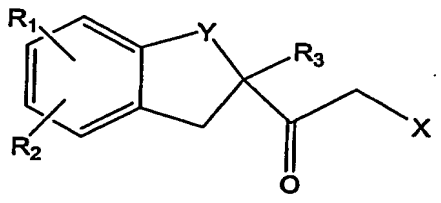
7. A process according to any of claims 1 to 6 wherein Y is $-CH_2-$, R_1 is F, R_2 is H and R_3 is ethyl.

8. A process for preparing a compound of formula (IV)



(IV)

wherein Y is $-CH_2-$ or $-CO-$, R_1 is H, halo or hydroxy, R_2 is H or halo and R_3 is H or lower alkyl, comprising reacting a compound of formula (III)



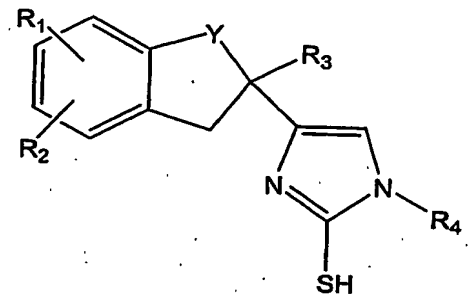
(III)

wherein Y, R_1, R_2 and R_3 are as defined above and X is halo, with an amine of formula R_4NH_2, wherein R_4 is an easily removable leaving group, and an alkali metal thiocyanate.

9. A process according to claim 8 comprising reacting a compound of formula (III) with benzylamine and potassium thiocyanate.

10. A process according to claim 8 or 9 wherein Y is $-CH_2-$, R_1 is F, R_2 is H and R_3 is ethyl.

11. A compound of formula (IV)

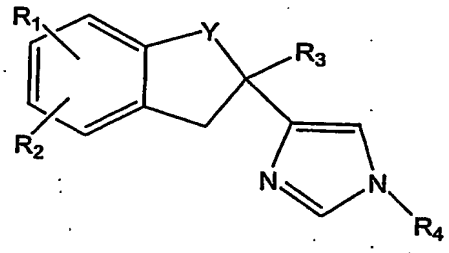


(IV)

wherein Y is $-CH_2-$ or $-CO-$, R_1 is halo or hydroxy, R_2 is H or halo, R_3 is H or lower alkyl and R_4 is an easily removable leaving group.

12. A compound according to claim 11 wherein Y is $-CH_2-$, R_1 is F, R_2 is H, R_3 is ethyl and R_4 is benzyl.

13. A compound of formula (V)



(V)

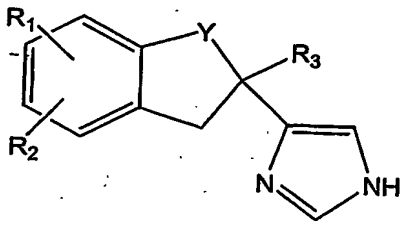
wherein Y is $-CH_2-$ or $-CO-$, R_1 is halo or hydroxy, R_2 is H or halo, R_3 is H or lower alkyl and R_4 is an easily removable leaving group.

14. A compound according to claim 13 wherein Y is $-CH_2-$, R_1 is F, R_2 is H, R_3 is ethyl and R_4 is benzyl.

L3

(57) Abstract

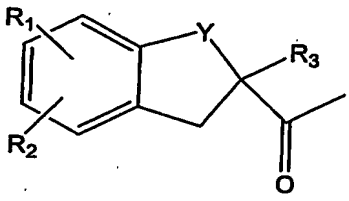
The invention relates to a process for preparing substituted imidazole derivatives of formula (I) and acid addition salts thereof



(I)

in which formula Y is $-CH_2-$ or $-CO-$, R_1 is H, halo or hydroxy, R_2 is H or halo and R_3 is H or lower alkyl, starting from

a compound of formula (II)



(II)

wherein Y, R_1, R_2 and R_3 are as defined above. The invention also relates to intermediates and their preparation.

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/FI04/000004

International filing date: 08 January 2004 (08.01.2004)

Document type: Certified copy of priority document

Document details: Country/Office: FI
Number: 20030026
Filing date: 08 January 2003 (08.01.2003)

Date of receipt at the International Bureau: 05 September 2005 (05.09.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)